## REMARKS

This amendment is responsive to the non-final Office Action mailed July 15, 2003. Claims 112-116 were pending and under consideration in the instant Application. In this amendment, Claims 112, 113, 115, and 116 are amended, and new Claims 117-131 are presented for consideration. Thus, following entry of the present amendment, Claims 112-131 will be pending and under consideration.

### I. The Amendment to the Claims

The present amendment amends Claims 112, 113, 115, and 116. The amendments to Claims 112, 113, 115, and 116 are fully supported by the specification and claims of the application as originally filed.

In particular, support for the amendments to Claim 112, 115, and 116 can be found, for example, in Claims 1, 55, and 57 as originally filed, in Claims 112, 115, and 116 as previously pending, and in the specification at page 40, line 10, to page 45, line 4, at page 66, lines 7-18, and at page 68, line 31 to page 69, line 10-20. Support for the amendment to Claim 113 may be found in Claim 4 as originally filed and in Claim 113 as previously pending.

Further, the present amendment adds new Claims 117-131 for consideration. New Claims 117-131 are fully supported by the specification and claims of the application as originally filed.

Specifically, support for new Claims 117, 122, and 127 can be found, for example, in Claim 6 as originally filed, and in the specification at page 59, lines 16-29 and at page 55, lines 15-21. Support for new Claims 118, 123, and 128 can be found, for example, in Claim 7 as originally filed and in the specification at page 54, lines 12-28 and at page 55, lines 15-21. Support for new Claims 119, 124, and 129 can be found, for example, in Claim 25 as originally filed and in the specification at page 55, lines 15-21. Support for new Claims 120, 125, and 130 can be found, for example, in Claim 26 as originally filed and in the specification at page 55, lines 15-21. Finally, support for new Claims 121, 126, and 131 can be found, for example, in Claim 14 as originally filed.

In view of the foregoing, Applicants respectfully submit that the amendments to Claims 112, 113, 115, and 116 and new Claims 117-131 are fully supported by the specification and claims of the application as originally filed. Accordingly, no new matter is introduced by the instant amendment. Therefore, Applicants hereby respectfully request entry of the present amendment under 37 C.F.R. § 1.111

## II. The Rejection of Claims 112-116 under 35 U.S.C. § 112, first paragraph

Claims 112-116 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable one of skill in the art to make and/or use the invention as presently claimed. In particular, Claims 112-115 stand rejected because the specification allegedly does not provide methods for determining if a viral population is susceptible to an anti-viral drug. Further, Claims 112-116 stand rejected because the specification allegedly does not enable the skilled artisan to practice methods for determining HCV susceptibility to anti-viral drugs that operate through means other than inhibiting viral replication. Applicants respectfully traverse the rejections on the grounds that the specification provides sufficient guidance for one of skill in the art to practice the full scope of the claimed methods with only routine experimentation.

### A. The Legal Standard

To satisfy 35 U.S.C. § 112, a specification must describe a claimed invention sufficiently to enable one of ordinary skill in the art to practice the invention without undue experimentation. *See In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). The multi-factor test summarized by the Federal Circuit in *Wands* forms the basis for an inquiry into whether an amount of experimentation is undue.

The *Wands* factors include (1) the quantity of experimentation necessary, (2) the amount of guidance provided, (3) the presence or absence of working examples, (4) the nature of the invention, (5), the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *See id.* The test for determining whether experimentation is undue is "not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine or the specification provides a reasonable amount of guidance with respect to ... the experimentation." *See Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (1982).

### B. The Specification Enables a Skilled Artisan to Assess the Susceptibility of a Viral Population to an Antiviral Drug

Contrary to the assertion of the PTO, the present application enables the skilled artisan to assess the susceptibility of a viral population to an antiviral drug with no more than routine experimentation. The methods recite that the host cells comprise a plurality of resistance test vectors, each of which comprises a patient-derived segment and an indicator gene. As discussed in the specification, the patient-derived segment comprises nucleic acid amplified from the population of viral RNA present in the patient. See the specification at

page 55, line 28, to page 56, line 3. As such, the plurality of resistance test vectors is representative of the viral population in the patient.

As also discussed in the specification and recited by the claims, the activity of the indicator genes present in the sample of host cells is dependent upon the patient-derived segment. Because of this relationship, an assessment of the activity of the indicator genes in the sample yields information concerning the viral population in the patient (*e.g.*, information concerning susceptibility of the HCV viral population in the patient for an HCV anti-viral drug, or anti-HCV drug resistance of the HCV population in the patient). Accordingly, when this method is performed in the presence of an antiviral drug, the skilled artisan can determine the effect of such a drug on the entire viral population, and not just one member of the population.

C. **The Specification Enables a Skilled Artisan to Determine HCV Susceptibility to Antiviral Drugs that do not Inhibit Viral Replication**

In addition, the susceptibility of the viral population can be determined for antiviral drugs that act through mechanisms other than inhibiting replication. The PTO asserts that the claimed methods only operate to determine viral susceptibility to antiviral drugs that inhibit viral replication, but not antiviral drugs that inhibit infection or cleavage of the HCV polyprotein. The PTO does not indicate any technical basis for this conclusion. Applicants respectfully disagree, and submit that the specification indeed teaches how susceptibility of viral populations to antiviral drugs that inhibit infection and/or protease activity can be assessed

Specifically, Applicants respectfully invite the PTO's attention to the specification at page 54, lines 21-28. Here, the specification teaches that, in certain embodiments, the indicator gene (luciferase) is inactive when it is part of the polyprotein, and becomes active when cleaved from the polyprotein by HCV protease. One of skill in the art can use such embodiments to assess the effectiveness of antiviral drugs that inhibit the HCV protease with only routine experimentation.

Further, the specification also teaches that, in embodiments where the indicator gene is active before cleavage from the polyprotein, viral particles should be isolated and used to infect a new target cells as part of a two cell assay. This system can be used to assess the susceptibility of such viral particles to antiviral drugs that inhibit infection, since the viral particles infect the target cells prior to detection of indicator gene activity. If infection is inhibited by the antiviral drug, the skilled practitioner will observe less indicator gene activity than would otherwise be expected

Accordingly, Applicants respectfully submit that the specification enables the skilled artisan to practice the full scope of the claimed invention. The skilled artisan can determine the susceptibility of an HCV viral population that is infecting a patient with the claimed methods, and such methods work to determine susceptibility to drugs that inhibit infection or cleavage of the HCV polyprotein. Therefore, Applicants respectfully submit that the rejection of Claims 112-116 under 35 U.S.C. § 112, first paragraph, as not enabled by the specification is in error and earnestly request its withdrawal.

## III. The Rejection of Claims 112-114 and 116 under 35 U.S.C. § 103(a)

Each of Claims 112-114 and 116 stands rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 6,127,116, issued to Rice *et al* ("*Rice*"). Further, Claim 115 stands rejected as allegedly obvious over *Rice* in view of U.S. Patent No. 5,576,177, to Friedland *et al.* ("*Friedland*") and Reissue Patent No. RE29,955, to Bornstein *et al.* ("*Bornstein*"). In response, Applicants respectfully submit that *Rice* does not teach each and every element recited by Claims 112-116 and that none of the cited references provide motivation or suggestion to modify *Rice* to result in the claimed methods. Accordingly, Applicants respectfully submit that the PTO cannot establish a *prima facie* case of obviousness of Claims 112-116, and the rejection of these claims on that basis should be withdrawn.

### A. The Legal Standard for Obviousness

To reject a claim as under 35 U.S.C. § 103(a), the PTO bears the initial burden of showing an invention to be *prima facie* obvious over the prior art. *See In re Bell*, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1992). If the PTO cannot establish a *prima facie* case of unpatentability, then without more the applicant is entitled to grant of the patent. *See In re Oetiker*, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992). The PTO must meet a three-part test to render a claimed invention *prima facie* obvious.

To begin with, the prior art references cited by the PTO must provide "motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant." *See In re Kotzab*, 55 U.S.P.Q.2d 1316 (Fed. Cir. 2000). Where one reference is relied upon by the PTO, there must be a suggestion or motivation to modify the teachings of that reference. *See id.* Where an obviousness determination rests or relies on the combination of two or more references, there must be some suggestion or motivation to combine the references. *See WMS Gaming Inc. v. International Game Technology*,

teachings within the references themselves, from the ordinary knowledge of one skilled in the art, or from the nature of the problem to be solved. *See id.*

Second, the prior art references cited by the PTO must suggest to one of ordinary skill in the art that the invention would have a reasonable expectation of success. *See In re Dow Chemical*, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). The expectation of success, like the motivation to combine two prior art references, must come from the prior art, not the applicant's disclosure. *See id.*

Finally, the PTO must show that the prior art references, either alone or in combination, teach or suggest each and every limitation of the rejected claims. *See In re Gartside*, 53 U.S.P.Q.2d 1769 (Fed. Cir. 2000). If any one of these three factors is not met, the PTO has failed to establish a prima facie case of obviousness and the applicant is entitled to grant of a patent without making any affirmative showing of non-obviousness.

**B. *Rice* does not Teach Each and Every Element of the Invention as Presently Claimed**

Claims 112-116 recite methods for assessing the susceptibility of an HCV viral population infecting a patient that comprises, *inter alia*, measuring activity of indicator genes in a sample of host cells. The indicator genes are encoded in a plurality of resistance test vectors, each of which comprises a patient-derived segment. The activity of the indicator genes depends on the patient-derived segments. As described above, the plurality of resistance test vectors is representative of the viral population infecting the patient. These resistance test vectors can be used to determine the susceptibility of such a viral population to an antiviral drug.

Nowhere does *Rice* teach or suggest any methods for determining the susceptibility of a viral population to an antiviral drug. Applicants gratefully acknowledge the PTO's concession that *Rice* does not teach such methods, but respectfully disagree with the PTO that *Rice* provides motivation or suggestion to modify its teaching so as to render the subject matter of Claims 112-116 obvious.

**C. *Rice* does not Provide Motivation or Suggestion to Modify its Teaching to Render Claims 112-116**

The PTO argues that *Rice's* teaching regarding the diversity of the HCV viral genome would motivate one of ordinary skill in the art to modify the methods of *Rice* to the methods of Claims 112-116. Specifically, the PTO contends that *Rice* "recognizes, and is partially reliant, on the existence and emergence of variant strains of HCV." However, the bases used

by the PTO to support this contention in no way indicate that *Rice* recognizes the possibility of multiple viral genotypes in a single individual.

For example, the PTO cites the paragraph spanning columns 1 and 2 of *Rice* as recognizing the diversity of the HCV viral genome and the emergence of resistant strains within an individual. This paragraph does indeed indicate that genetic variants of HCV can emerge from chronically infected individuals, but it does not teach that more than one such genetic variant can be isolated from a single patient. Rather, this paragraph merely recognizes that different strains of HCV exist.

Similarly, the PTO cites *Rice* at column 12, lines 9-17, as recognizing the presence of adaptive mutations within an HCV strain. Again, this passage merely demonstrates *Rice's* recognition of the genetic diversity of HCV, not teaching that more than one genetic variant of HCV may be isolated from a single patient, and certainly does not suggest testing multiple variants from a single patient. Indeed, this passage of *Rice* focuses on selecting strains of HCV having adaptive mutations that permit high level replication of the HCV isolate in cell culture or animal models, which was a goal of *Rice*. It does not even indicate that such adaptive mutations may be present in an HCV strain isolated from a patient, let alone that such a strain may co-infect the patient together with one or more additional HCV quasispecies. Thus, even though *Rice* recognizes the diversity of the HCV genome - diversity being a feature of all genomes - *Rice* nonetheless provides no motivation to modify the teaching therein to render the presently claimed methods obvious.

The PTO rejected Claim 115 as obvious over *Rice* in view of *Fridland* and *Bornstein*, relying on the secondary references to teach comparing the results of an assay to a standard curve rather than a contemporaneous control. However, neither *Fridlan* nor *Bornstein*, alone or in combination, remedies the defects of *Rice* noted above. Because Claim 115 recites a method for determining anti-HCV drug resistance of a HCV viral population in a patient, whatever teaching *Fridland* and *Bornstein* may provide regarding use of a standard curve is immaterial to the patentability of Claim 115, since, as shown above, *Rice* neither teaches nor suggests any such methods.

Applicants note that the PTO has indicated that the previously pending claims are anticipated under § 102(e) by *Rice*, but that the PTO did not explicitly reject the claims on that basis. Applicants believe that Claims 112-116, both as amended and as previously pending, are in fact novel over *Rice*, and earnestly request the PTO to make clear for the record that *Rice* does not anticipate the invention as presently claimed.

In view of the foregoing, Applicants respectfully submit that none of Claims 112-131 are obvious over *Rice*, either alone or in combination the cited secondary references, since each of Claims 112, 115, and 116 are not obvious over *Rice* as shown above, and each of Claims 113, 114, and 117-131 depend from one of these non-obvious claims. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103(a).

## IV. The Rejection of Claims 112-116 under the Judicially-Created Doctrine of Obviousness-Type Double Patenting

Claims 112-116 stand rejected under the judicially-created doctrine of obviousness-type double patenting over Claims 1, 4, 7-11, 13, 14, 46-49, 51-53, 70-73, and 78-83 of U.S. Patent No. 5,837,464 ("the '464 patent") in view of Lu *et al.* ("*Lu*") and Wang *et al.* ("*Wang*") and over Claims 1, 2, 18, 24-27, and 30-42 of U.S. Patent No. 6,242,187 ("the '187 patent") in view of Lu *et al.* and Wang *et al.* Applicants respectfully submit that the rejection of Claims 112-116 is in error because none of the rejected claims is an obvious variant of any claim of the '464 patent or the '187 patent.

### A. The Legal Standard

Under the judicially-created doctrine of obviousness-type double patenting, a claim must be patentably distinct from a claim of an already issued patent or pending application. *See General Food Corp. v. Studiengesellshaft Kohle mbH*, 23 U.S.P.Q.2d 1839 (Fed. Cir. 1992). If the claim at issue defines more than an obvious variation of the patented or pending claim, it is patentably distinct and rejection of the claim under the doctrine of obviousness-type double patenting is improper. *See id.* To establish a proper obviousness-type double patenting rejection, the Examiner must show that the claim at issue is a "mere variation" of the patented or pending claim that "would have been obvious to those of ordinary skill in the relevant art." *See In re Kaplan*, 229 U.S.P.Q. 678, 683 (Fed. Cir., 1986). Finally, where the claim at issue is alleged to be an obvious variant of a currently pending claim, a rejection on these grounds is provisional. *See* M.P.E.P. § 804 I.B. If such a provisional rejection is the last remaining issue preventing passage of the rejected claim to issuance, the rejection should be removed and the claim in the other pending application should be non-provisionally rejected. *See id.*

B. **Claims 112-116 are not Obvious Variants of any Claim of the '464 Patent or the '187 Patent**

As described above, Claims 112-116 are directed to methods for determining susceptibility of an HCV viral population infecting a patient to an antiviral drug. In contrast, the claims of the '464 patent are directed to methods for determining susceptibility of HIV to anti-HIV drugs. No claim of the '464 patent even remotely suggests that the methods claimed therein could be applied to either individual HCV isolates or to HCV viral populations. Similarly, the claims of the '187 patent are directed to methods for determining the susceptibility of HBV to anti-HBV drugs. No claim of the '187 patent suggests that these methods could be modified to methods suitable for determining the susceptibility of HCV populations to antiviral drugs.

Moreover, neither *Lu* nor *Wang* can properly be combined with either the '464 patent or the '187 patent to show that Claims 112-116 are obvious variants of any claim of these patents. As described above, *Lu* and *Wang* can only be used to show that one of ordinary skill in the art would view the claims of the present application as obvious variants of the claims of the '464 patent or the '187 patent. *Lu* and *Wang* show no such thing. *Lu* and *Wang* provide no teaching or suggestion that a method for determining susceptibility of HIV or HBV to antiviral drugs could or should be adapted to methods for determining susceptibility of an HCV viral population to antiviral drugs. As such, *Lu* and *Wang* surely fail to teach or suggest that one of only ordinary skill in the art would regard such methods for determining susceptibility of HCV viral populations to antiviral drugs as obvious variants of the methods claimed by the '464 patent or the '127 patent.

In view of the foregoing, Applicants respectfully submit that Claims 112-116 are not obvious variants of any claim of the '464 patent or the '187 patent. Accordingly, Applicants respectfully suggest that the rejection of Claims 112-116 under the judicially-created doctrine of obviousness-type double patenting is in error, and earnestly request its withdrawal.

V. **The Provisional Rejection of Claims 112-114 under the Judicially-Created Doctrine of Obviousness-Type Double Patenting**

Claims 112-114 stand provisionally rejected under the judicially-created doctrine of obviousness-type double patenting over Claims 1, 2, 5, and 6 of co-pending Application No. 10/139,069 ("the '069 application"). Applicants believe that this rejection is the last remaining issue before passage of Claims 112-114 to issuance. Without acquiescing to the propriety of the rejection, Applicants respectfully request that Claims 112-114 be allowed to

issue, and that this rejection be made non-provisionally in connection with the '069 application. *See* M.P.E.P. § 804 I.B.

## VI. Reference to Related, Co-Pending U.S. Applications

For the PTO's convenience, Applicants hereby identify all applications currently pending before the United States Patent and Trademark Office that are related to the present application.

| Application No. | Attorney Docket No. | Filing Date | Art Unit | Examiner |
|---|---|---|---|---|
| 08/875,082 | 11068-051-999 | June 6, 2001 | 1636 | J. Ketter |
| 10/139,069 | 11068-010-999 | May 3, 2002 | 1648 | D. Wortman |

Application No. 10/139,069 is a continuation-in-part of the present application.

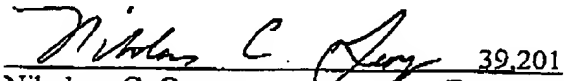
## CONCLUSION

In light of the above amendments and remarks, Applicants respectfully submit that Claims 112-131 satisfy all the criteria for patentability and are in condition for allowance. Accordingly, Applicants respectfully request that the Examiner reconsider this application with a view towards allowance and solicit an expeditious passage of Claims 112-131 to issuance. The Examiner is invited to call the undersigned attorney at (212) 790-9090, if a teleconference could help resolve any remaining items.

Pursuant to 37 CFR § 1.136(a)(3), the Commissioner is authorized to charge all required fees, fees under 37 CFR § 1.17 and all required extension of time fees, or credit any overpayment, to Pennie & Edmonds LLP U.S. Deposit Account No. 16-1150 (order no. 011068-0043-999).

Respectfully submitted,

Date: January 14, 2004



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